

滇乌碱的结构改造

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摘要 滇乌碱是云南乌头属植物中分布最广、含量最高的一种二萜生物碱成分, 但其毒性高。为了充分利用这一丰富的资源, 我们用滇乌碱为起始物合成了7个衍生物。本文对衍生物合成的方法及合成产物的光谱数据作了报道。

关键词 滇乌碱, 滇乌碱衍生物, 结构修饰

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Structural Modification of Yunaconitine

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Abstract Yunaconitine, a diterpenoid alkaloid native to Yunnan in the plants of *Aconitum* species, is the richest in content and the widest in distribution, but its toxicity is high. In order to utilize the rich resource, some structural modification from yunaconitine had been undertaken, and seven derivatives have been got. This paper reports the synthetic ways of these derivatives and their spectra.

Key words Yunaconitine, Derivatives of yunaconitine, Structural modification

Among diterpenoid alkaloids found in the plants of *Aconitum* species native to Yunnan, China, yunaconitine (1) is the richest in content and the widest in distribution (Chen, 1979). But its toxicity is also high [LD₅₀ 585 μg/kg (i. p. in mouse), LD₁₀₀ 50 μg/kg (i. v. in rat)]. In order to utilize the rich resource, some structural modification from yunaconitine had been undertaken.

In the course of transformation of A - ring, we made a plan to synthesize yunaconitinone (2) and yunaconitoline (4) from yunaconitine.

It has long been known that aconitine, a similar *Aconitum* diterpenoid alkaloid to yunaconitine, is oxidized by chromic acid to the ketone aconitinone, which very readily loses the elements of methanol and gives rise to an α, β - unsaturated ketone, aconitoline (Majima *et al.*, 1936; Jacobs *et al.*, 1940). Mayer *et al.* (1959), who also prepared aconitoline, claimed that oxidation with chromic acid always gave aconitoline directly.

Our researches have confirmed that the oxidative product of yunaconitine (1) with chromic acid

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was yunaconitinone(**2**) , but **2** could convert to yunaconitoline(**4**) simply by subjecting to silica gel column and eluted with chloroform-ethyl acetate. These conclusions were supported by following evidence.

Yunaconitinone(**2**) , cubic crystal (acetone - hexane) , exhibited a base peak at 658[(M + 1)⁺] in FABMS (positive) . Its molecular formula was determined as C₃₅H₄₇O₁₁N by combination of FABMS and DEPT spectrum. The ¹H NMR showed the signal of 3.58(dd, 4.0, 8.0, 3 β - H) in yunaconitine (**1**) disappeared in yunaconitinone(**2**) . Meanwhile, the ¹³C NMR showed also the disappearance of 71.4(C - 3, **1**) in yunaconitinone(**2**) , and an additional signal of 214.2(C = O) appeared in **2**. The chemical shifts of 42.4(C - 2) , and 53.4(C - 4) in yunacotinone, which was caused by β - effect and downshifted from 33.5(C - 2, **1** and 43.1(C - 4, **1**) , respectively, also suggested the structure of yunaconitinone as **2**.

Yunaconitoline(**4**) , cubic crystal (acetone-hexane) , had the base peak at 626[(M + 1)⁺] . Its molecular formula was determined as C₃₄H₄₃O₁₀N by means of FABMS and DEPT spectrum. The IR spectrum showed bands at 1716 cm⁻¹ (ester) , 1663 cm⁻¹ (carbonyl) and 818 cm⁻¹ (double bond) . The ¹H NMR spectrum exhibited an additional double bond signals at 6.42(1H, d, 10.3) and 6.22 (1H, d, 10.3) , as well as the disappearance of 1 α - OCH₃ in 3.09 (s, 3H) of **1** . The ¹³C NMR spectrum showed also a double bond at 146.6(d) , 132.1(d) , and a carbonyl bond at 200.2(s) . These evidence indicated that a six-membered α , β - unsaturated ketone had been formed . So, the structure of yunaconitoline could be **4** .

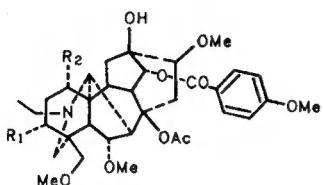
Another ketone compound was also obtained when **1** was converted to **2** . This compound had the similar ¹H, ¹³C NMR spectral data to those of **2** , except for the disappearance of ethyl group at N. So, the structure of this ketone compound, named as N - deethyl yunaconitinone, was determined as **3** .

Like the similar transformation of **2** to **4** , **3** was also subject to silica gel column and eluted with chloroform - ethyl acetate. But no α , β - unsaturated ketone compound like **4** formed from **2** was obtained as expected. This result implied that ethyl group at N had the ortho - effect to the process.

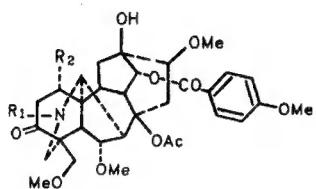
4 was then catalytically hydrogenized by Pt - C, absorbed 1 mol of hydrogen to produce compound **5.5** had still the carbonyl bond(¹³C - NMR: 217. 1) , but the double bond had been saturated. Its structure could be deduced as **5** .

5 was further reduced by sodium borohydride to give a reduced compound **6** . In comparison with **5** , **6** had no carbonyl bond, but an additional carbon substituted by a hydroxyl group appeared [¹³C NMR: 74.1(d)]. The hydroxyl group was deduced at C - 3 position with α - configuration on the basis of stereochemical model and ¹H NMR evidence [3.70(dd, 8.0, 16.0)]. It has been demonstrated that the A - ring hydroxyl and methoxyl groups were removed in these conversion from **1** to **6** .

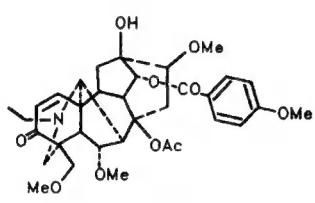
Pyrolysis of yunaconitine (**1**) gave a C₈ - C₁₅ olefinic compound, pyroyunaconitine(**8**) , [¹H NMR: 5.53(1H, 6.3, C - 15 - H); ¹³C NMR: 147.0(s, C - 8) , 116.5(d, C - 15)]. In the routine method, yunaconitine was esterified by acetic anhydride in pyridine to afford a mono acetylated compound, 3 - O - acetyl yunaconitine(**7**) .



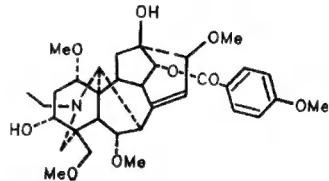
1 $R_1=OH, R_2=OMe$, Yunaconitine
 6 $R_1=OH, R_2=H$, 1-Demethoxyunaconitine
 7 $R_1=OAc, R_2=OMe$, 3-O-Acetylunaconitine



2 $R_1=Et, R_2=OMe$, Yunaconitinone
 3 $R_1=H, R_2=OMe$, N-Deethylunaconitinone
 5 $R_1=Et, R_2=H$, 1-Demethoxyunaconitinone



4 Yunaconitoline



8 Pyroyunaconitine

Experimental

Melting points were uncorrected. 1H and ^{13}C - NMR were recorded at 400 and 100.16MHz, respectively, using TMS as int. standard. IR were taken for KBr disc. Optical rotations were recorded on SEPA - 300. UV were measured in MeOH. FABMS (Positive) and EIMS were measured with VG Auto Spec - 3000 mass spectrometer.

Yunaconitinone and N - Deethylunaconitinone

Chromium trioxide(1.01 g) in cold acetone(12 mL) was added to yunaconitine(1.28 g) in cold acetone(20 mL). The reaction mixture was stirred at room temperature for 8 hours. after which the solvent was evaporated under reduced pressure. The dark brown residue was triturated with 10% sodium carbonate, extracted with ether (500 mL).

Dried with anhydrous sodium sulphate, filtered and evaporated to dryness, the ether solution resulted in white powdered yunaconitinone(0. 98 g) which was crystallized in the contact with acetone and n - hexane to consist of colorless cubic crystals, mp. 206.5 ~ 208.5°C, λ_{nm}^{MeOH} : 203(ε,20400), 207.5 (ε,19000), 257.5(ε,22400). ν_{max}^{KBr} cm⁻¹: 1714(C=O). $[\alpha]_D^{21} - 36.36^\circ(c,0.11,CHCl_3)$. FABMS (positive): 658 [(M + 1)⁺, 64%], 598(658 - AcOH, 12%). ^{13}C NMR data see Table 1.

The mother liquor, purified by chromatography of silica gel, eluted with chloroform: ethyl acetate 7:3, yielded white powdered N - deethylunaconitinone(0.17g), mp. 153.0 ~ 155.5°C, ν_{max}^{KBr} cm⁻¹: 1710 - 1719, FABMS(positive): 630[(M + 1)⁺, 100%]. ^{13}C NMR data see Table 1.

Yunaconitoline

Yunaconitinone(60 mg) was placed on silica gel column. After the alkaloid was eluted with chloroform: ethyl acetate 7:3, yunaconitoline(54 mg) was yielded in powdered form which could be recrystallized from acetone: n - hexane to afford cubic crystals, mp. 225.0 ~ 227.0°C. $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 203.5(ε, 21300), 208(ε, 20600), 256(ε, 24500). $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1663(C = O), 818(C = C). [α]_D²⁴ + 87.32°(c, 0.355, CHCl₃). FABMS(positive): 626[(M + 1)⁺, 100%], 566(626 - AcOH, 58%). ¹H NMR: 6.42(d, 10.3, 1 - H), 6.22(d, 10.3, 2 - H). ¹³C NMR data see Table 1.

1 - Demethoxyyunaconitinone

Yunaconitoline(178 mg) was dissolved in 75% EtOH, and palladium carbon catalyst (74 mg) was added. The solution was stirred at room temperature under hydrogen atmosphere for 18 hrs, then filtered. The filtrate was evaporated to give white powdered 1 - Demethoxyyunaconitinone(170 mg), mp. 126.0 ~ 129.0°C, FABMS(positive): 628[(M + 1)⁺, 100%], 568(628 - AcOH, 47%), 469(17%), 301(88%). ¹³C NMR data see Table 1.

1 - Demethoxyyunaconitine

Sodium borohydride (900 mg) was added four times in 6 hrs to a solution of 1 - demethoxyyunaconitinone(250 mg) in MeOH(10 mL). The mixture was stirred at room temperature for 10 hrs. The resulting mixture was evaporated to a little volume, poured into water, and extracted with chloroform. The extract was washed three times with water, dried with sodium sulfate, and evaporated under reduced pressure to afford a white powdered 1 - demethoxyyunaconitine (234 mg), mp. 123.0 ~ 126.5°C, FABMS(positive): 630[(M + 1)⁺, 97%], 570(630 - AcOH, 100%). ¹H NMR: 3.70(dd, 8.0, 16.0, 3β - H). ¹³C NMR data see Table 1.

Pyroyunaconitine

Yunaconitine(100 mg) was heated under reduced pressure(20 mm) during 15 min at 180 ~ 188°C (air bath). The product was dissolved in chloroform, chromatographed on a short column of silica gel, and eluted with petroleum ether: acetone 7:3. Evaporation of the elutate gives rise to a powdered pyroyunaconitine (54 mg), mp. 135.0 ~ 137.0°C, $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 912(C = C). EIMS(70eV): 599(M⁺, 0.8%), 568(1.3%), 135(100%). ¹H NMR: 5.53(d, 6.3, C - 15 - H). ¹³C NMR data see Table 1.

3 - O - Acetyl yunaconitine

In a routine method, yunaconitine(20 mg), freshly distilled acetic anhydride(6.5 mL) and pyridine(5 mL) was kept at room temperature for 18 hrs. The reaction mixture was acidified with 2% HCl to pH 4, and alkalized with ammonia liquor to pH 9, respectively. The solution was then extracted with chloroform. Evaporation of the extract left the crude product (22 mg) which after recrystallization from acetone: cyclohexane afforded crystalline 3 - O - acetyl yunaconitine (19 mg), mp. 168.0 ~ 171.0°C, EIMS(70eV): 701(M⁺, 17%), 670(57%), 643(57%), 610(62%). ¹H NMR: 3.79(d, 11.5). ¹³C NMR data see Table 1.

Table 1 ^{13}C NMR chemical shifts and assignments*

Carbon	1	2	3	4	5	6	7	8
1	83.1	83.0	84.9	146.6	38.6	29.6	83.4	83.7
2	33.5	42.4	43.5	132.1	25.4	29.1	32.0	33.3
3	71.4	214.2	217.9	200.2	217.1	74.1	71.7	71.9
4	43.1	53.4	56.5	N.R	53.2	43.2	42.5	44.1
5	47.4	44.2	55.0	48.7	48.3	48.9	46.5	48.3
6	82.2	81.1	82.3	82.2	82.9	83.3	81.8	83.1
7	44.7	44.9	44.8	43.8	44.4	44.2	45.3	48.2
8	85.6	85.7	86.6	85.7	85.9	85.7	85.5	147.0
9	48.7	47.8	45.5	49.4	44.1	48.7	49.5	49.8
10	40.8	41.3	40.9	37.4	40.2	40.7	40.6	46.5
11	50.2	50.0	52.0	51.0	45.7	46.1	50.0	51.7
12	35.1	34.5	37.1	38.1	37.4	37.1	35.7	38.2
13	74.6	74.7	76.2	74.8	74.7	74.7	74.9	71.9
14	78.5	78.6	80.3	78.7	78.6	78.7	78.5	78.2
15	39.5	40.4	41.5	40.3	40.5	40.2	39.4	116.5
16	83.5	83.5	83.9	83.8	83.8	83.9	83.8	83.7
17	61.6	61.2	59.5	61.0	65.0	64.1	61.3	N.R
18	76.7	75.8	77.1	71.9	75.5	76.7	71.8	77.9
19	48.7	53.0	46.3	51.4	52.9	48.9	48.9	49.9
N-CH ₂	47.4	47.8	—	48.7	48.5	47.2	47.7	48.1
CH ₃	13.1	12.6	—	12.9	13.2	13.3	13.7	13.5
1'	55.7	56.0	56.1	—	—	—	56.2	56.3
6'	58.7	58.8	58.6	59.0	59.0	58.9	58.8	58.1
16'	57.7	57.9	56.1	59.0	57.9	57.6	58.1	57.3
18'	59.0	59.0	59.7	59.0	59.1	59.1	58.8	59.3
C=O	169.9	169.8	171.1	170.2	169.8	169.8	169.8	—
CH ₃	21.5	21.5	21.7	21.5	21.9	21.6	21.6	—
C=O	166.1	165.8	167.4	165.8	165.8	165.8	166.1	168.2
	122.5	122.5	123.5	122.7	122.5	122.6	122.7	123.1
C ₆ H ₄	131.6	131.6	132.9	131.7	131.7	131.7	131.7	132.0
	113.7	113.8	115.0	113.9	113.9	113.8	113.8	113.5
	163.5	163.6	165.0	163.7	163.6	163.5	163.5	163.4
OCH ₃	55.3	55.4	55.0	55.5	55.5	55.4	55.4	55.4

Chemical shifts (δ) in ppm relative to TMS in CDCl_3

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